A novel clinical score (InterTAK Diagnostic Score) to differentiate takotsubo syndrome from acute coronary syndrome: results from the International Takotsubo Registry

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Abstract: AIMS: Clinical presentation of takotsubo syndrome (TTS) mimics acute coronary syndrome (ACS) and does not allow differentiation. We aimed to develop a clinical score to estimate the probability of TTS and to distinguish TTS from ACS in the acute stage. METHODS AND RESULTS: Patients with TTS were recruited from the International Takotsubo Registry (www.takotsubo-registry.com) and ACS patients from the leading hospital in Zurich. A multiple logistic regression for the presence of TTS was performed in a derivation cohort (TTS, n = 218; ACS, n = 436). The best model was selected and formed a score (InterTAK Diagnostic Score) with seven variables, and each was assigned a score value: female sex 25, emotional trigger 24, physical trigger 13, absence of ST-segment depression (except in lead aVR) 12, psychiatric disorders 11, neurologic disorders 9, and QTc prolongation 6 points. The area under the curve (AUC) for the resulting score was 0.971 [95% confidence interval (CI) 0.96-0.98] and using a cut-off value of 40 score points, sensitivity was 89% and specificity 91%. When patients with a score of 50 were diagnosed as TTS, nearly 95% of TTS patients were correctly diagnosed. When patients with a score 31 were diagnosed as ACS, 95% of ACS patients were diagnosed correctly. The score was subsequently validated in an independent validation cohort (TTS, n = 173; ACS, n = 226), resulting in a score AUC of 0.901 (95% CI 0.87-0.93). CONCLUSION: The InterTAK Diagnostic Score estimates the probability of the presence of TTS and is able to distinguish TTS from ACS with a high sensitivity and specificity. TRIAL REGISTRATION: NCT0194762.

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Aims Clinical presentation of takotsubo syndrome (TTS) mimics acute coronary syndrome (ACS) and does not allow differentiation. We aimed to develop a clinical score to estimate the probability of TTS and to distinguish TTS from ACS in the acute stage.

Methods and results Patients with TTS were recruited from the International Takotsubo Registry (www.takotsubo-registry.com) and ACS patients from the leading hospital in Zurich. A multiple logistic regression for the presence of TTS was performed in a derivation cohort (TTS, $n = 218$; ACS, $n = 436$). The best model was selected and formed a score (InterTAK Diagnostic Score) with seven variables, and each was assigned a score value: female sex 25, emotional trigger 24, physical trigger 13, absence of ST-segment depression (except in lead aVR) 12, psychiatric disorders 11, neurologic disorders 9, and QTc prolongation 6 points. The area under the curve (AUC) for the resulting score was 0.971 [95% confidence interval (CI) 0.96–0.98] and using a cut-off value of 40 score points, sensitivity was 89% and specificity 91%. When patients with a score of ≥50 were diagnosed as TTS, nearly 95% of TTS patients were correctly diagnosed. When patients with a score ≤31 were diagnosed as ACS, ~95% of ACS patients were diagnosed correctly. The score was subsequently validated in an independent validation cohort (TTS, $n = 173$; ACS, $n = 226$), resulting in a score AUC of 0.901 (95% CI 0.87–0.93).

Conclusion The InterTAK Diagnostic Score estimates the probability of the presence of TTS and is able to distinguish TTS from ACS with a high sensitivity and specificity.
Trial registration: NCT0194762

Keywords Takotsubo (stress) syndrome • Broken heart syndrome • Acute coronary syndrome • Clinical score • Disease prevalence

Introduction

Takotsubo syndrome (TTS) is an acute heart failure condition characterized by acute LV dysfunction with distinct wall motion abnormalities.[1–3] Patients with TTS often present with symptoms similar to those of acute coronary syndrome (ACS) such as chest pain and dyspnoea.[1,4] In addition, ECG and cardiac biomarkers including troponin and creatine kinase are commonly changed in both entities.[5–7] As such, clinical presentation on admission is commonly indistinguishable from classical ACS.[8,9] Based on currently available data, TTS is estimated to occur in 2% of all patients with ACS.[8] However, TTS is still underestimated,[10] and may actually occur at a higher incidence.

Recently, we have demonstrated that in-hospital outcome of TTS is comparable with that of ACS,[1] which indicates that TTS is not as benign as previously assumed but is in fact a serious and life-threatening condition. Early cardiac catheterization is necessary to make a correct diagnosis and remains the reference standard diagnostic test for TTS as for most patients with ACS.[11] Non-invasive clinical parameters are urgently needed to identify those patients, who present with the clinical picture of ACS but instead suffer from TTS.

The aim of the present study was to develop a sensitive and specific score to estimate the probability of TTS and to distinguish TTS from ACS in its initial clinical presentation in the emergency room.

Methods

Study patients and score generation

This substudy included patients from the recently published International Takotsubo Registry (InterTAK Registry; www.takotsubo-registry.com).[1,12] Patients with TTS were included in the present study if they met modified Mayo Clinic diagnostic criteria:[1,8] (i) systolic and diastolic LV wall motion impairment; (ii) absence of angiographic evidence of plaque rupture; absence of obstructive coronary artery disease (CAD) which is responsible for the respective wall motion abnormality; (iii) ECG abnormalities or increased troponin values; and (iv) absence of myocarditis/pheochromocytoma. Exceptions to the criteria include: (i) concomitant CAD was not an exclusion criterion; (ii) patients with focal TTS matching all other criteria, in whom the wall motion abnormality was congruent with a single coronary artery territory, were not excluded; and (iii) patients who died in the acute setting before confirmation of wall motion recovery were not excluded. When eligibility for inclusion was unclear, cases were studied by all members of the TTS team investigators in order to reach consensus.

To generate the InterTAK Diagnostic Score, a univariate analysis was performed in a derivation cohort (218 TTS patients vs. 436 ACS patients from the Zurich ACS Registry, 1:2 random assignment). From those parameters, which were significantly different between TTS and ACS and can be easily obtained in the emergency room without any imaging modality or laboratory values, seven were selected to build the score, as described in the statistical analysis section. Thereafter, the score was validated in an independent validation cohort (TTS, $n = 173$; ACS, $n = 226$) consisting of prospectively enrolled TTS patients from the InterTAK Registry and ACS patients from the Zurich ACS Registry.

Statistical analysis

For comparison of patients' characteristics between TTS and ACS in the derivation cohort Pearson χ^2 test for nominal data, paired Student's *t*-test, or Mann–Whitney U-test for continuous data were used. In order to develop a score for predicting the diagnosis of TTS, a logistic regression with the following potential predictors was performed in the

Table 1 Characteristics of patients from the derivation cohort[a]

Baseline characteristics	Takotsubo syndrome ($n = 218$)	Acute coronary syndrome ($n = 436$)	*P*-value
Demographics			
Female sex, *n* (%)	206/218 (94.5)	103/436 (23.6)	<0.001
Age, years, mean ± SD	67.3 ± 13.2 ($n = 218$)	63.4 ± 12.1 ($n = 436$)	<0.001
Triggering factors, *n* (%)			
Physical	109/218 (50.0)	89/436 (20.4)	<0.001
Emotional	93/218 (42.7)	11/436 (2.5)	<0.001
Both emotional and physical trigger	19/218 (8.7)	0/436 (0.0)	<0.001
No evident trigger	37/218 (17.0)	336/436 (77.1)	<0.001
Takotsubo syndrome type, *n* (%)			
Apical type	168/218 (77.1)		
Midventricular type	43/218 (19.7)		
Basal type	5/218 (2.3)		
Focal type	2/218 (0.9)		
Acute coronary syndrome type, *n* (%)			
STEMI		235/436 (53.9)	
NSTEMI		163/436 (37.4)	
Unstable angina pectoris		38/436 (8.7)	
Symptoms on admission, *n* (%)			
Chest pain	148/218 (67.9)	385/436 (88.3)	<0.001
Dyspnoea	113/218 (51.8)	110/436 (25.2)	<0.001
Cardiac biomarkers on admission, median (IQR)			
Troponin, factor increase in ULN[b]	6.67 (2.50–19.00) $n = 199$	3.75 (0.68–15.84) $n = 378$	0.003
Creatine kinase, factor increase in ULN	0.81 (0.48–1.42) $n = 139$	1.17 (0.61–3.16) $n = 397$	<0.001
BNP, factor increase in ULN[c]	5.14 (1.67–13.17) $n = 107$	1.69 (0.54–6.44) $n = 253$	<0.001
Inflammatory markers on admission, median (IQR)			
CRP, mg/L	5.40 (1.85–15.50) $n = 125$	3.65 (1.20–9.73) $n = 362$	0.06
WBC, $10^3/\mu L$	10.05 (7.51–13.21) $n = 201$	10.16 (8.17–12.93) $n = 397$	0.39
ECG on admission, *n* (%)			
Sinus rhythm	206/218 (94.5)	417/436 (95.6)	0.52
Atrial fibrillation	12/218 (5.5)	19/436 (4.4)	0.52
ST-segment elevation	94/218 (43.1)	202/436 (46.3)	0.44
ST-segment depression	23/218 (10.6)	126/436 (28.9)	<0.001
T-wave inversion	77/218 (35.3)	102/436 (23.4)	0.001
Left bundle branch block	11/218 (5.0)	16/436 (3.7)	0.40
QTc prolongation	83/218 (38.1)	111/436 (25.5)	0.001
Vital signs, mean ± SD			
Heart rate, b.p.m.	87.6 ± 23.0 ($n = 205$)	73.3 ± 14.8 ($n = 336$)	<0.001
Systolic blood pressure, mmHg	128.6 ± 31.8 ($n = 209$)	128.8 ± 25.6 ($n = 401$)	0.92
Diastolic blood pressure, mmHg	74.1 ± 18.4 ($n = 209$)	71.7 ± 13.7 ($n = 401$)	0.10
Cardiovascular risk factors, *n* (%)			
Hypertension	142/218 (65.1)	243/436 (55.7)	0.021
Diabetes mellitus	27/218 (12.4)	69/436 (15.8)	0.24
Current smoking	77/218 (35.3)	239/436 (54.8)	<0.001
Hypercholesterolaemia	76/218 (34.9)	161/436 (36.9)	0.61
Positive family history	68/218 (31.2)	99/436 (22.7)	0.019
Comorbidities, *n* (%)			
Cancer	39/218 (17.9)	48/436 (11.0)	0.015
COPD or asthma	32/218 (14.7)	23/436 (5.3)	<0.001
Neurologic disorders[d]	76/218 (34.9)	31/436 (7.1)	<0.001
Psychiatric disorders[d]	115/218 (52.8)	42/436 (9.6)	<0.001
Affective disorders[d]	63/218 (28.9)	24/436 (5.5)	<0.001

BNP, brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; ECG, electrocardiogram; IQR, interquartile range; NSTEMI, non-ST-segment elevation myocardial infarction; QTc, QT interval corrected for heart rate; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction; ULN upper limit of normal; WBC, white blood cell count.

[a]Depicted are the cohorts of patients with takotsubo syndrome and acute coronary syndrome: 1:2 random assignment.

[b]Including upper limits of the normal range for troponin T, high-sensitivity troponin T, and troponin I.

[c]Including upper limits of the normal range for BNP and NT-proBNP.

[d]Including patients with either acute/former/chronic disorders.

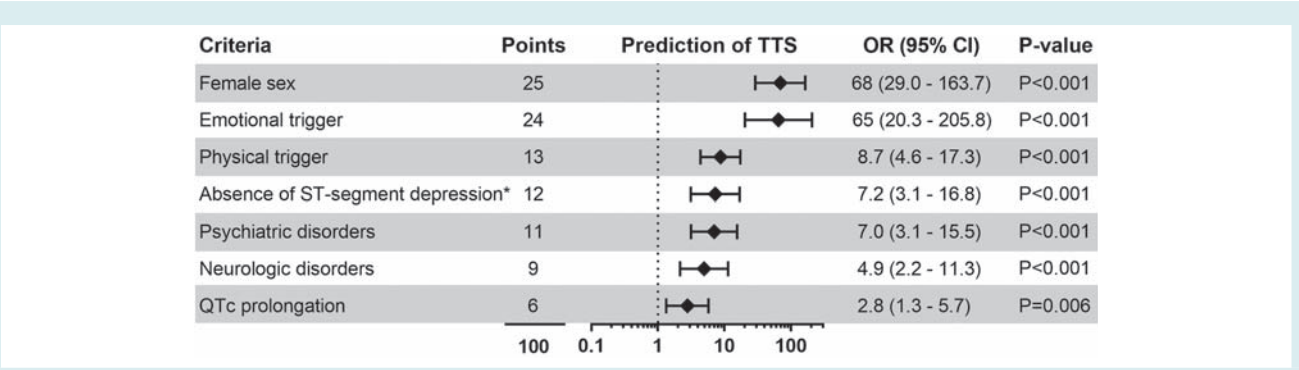

Figure 1 Clinical predictors for the diagnosis of takotsubo syndrome (TTS). Multiple logistic regression analysis. Odds ratios (OR) of the parameters female sex, emotional trigger, physical trigger, absence of ST-segment depression, psychiatric disorders, neurologic disorders, and QTc prolongation, which were chosen to build the InterTAK Diagnostic Score. Error bars demonstrate the 95% confidence interval (CI). *Except in lead aVR.

derivation cohort: female sex, age, physical trigger, emotional trigger, ST-segment elevation, ST-segment depression, T-wave inversion, left bundle branch block, QTc prolongation, cancer, COPD/asthma, neurologic disorders, psychiatric disorders, and affective disorders. The bestglm package[13] in R (version 2.15.1) was used for model selection with the Bayesian information criterion. We then developed a score by scaling and rounding the regression coefficients of the resulting multiple regression model.

A receiver operating characteristic (ROC) curve analysis, that reported the area under the curve (AUC) with a 95% confidence interval (CI), was performed to illustrate the predictive performance of the score.

A univariate logistic regression with the score as predictor was performed to develop a formula for the probability of TTS conditional on the score. The conditional odds in the derivation cohort is odds = exp (intercept + coefficient × score) and the corresponding probability is odds/(1 + odds).

The predictive performance of the score in the validation cohort was assessed using the AUC, and the calibration was assessed by comparing the observed proportion with the predicted probability. As the predicted probability depends on the prevalence, the conditional odds were adjusted accordingly: conditional odds in new cohort = conditional odds in derivation cohort × overall odds in new cohort/overall odds in derivation cohort.

A two-sided *P*-value ≤0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics, version 21.0 (IBM Corp., Armonk, NY, USA). Graphs were compiled with Prism 6 (GraphPad, La Jolla, CA, USA).

Results

Study groups

Patients with TTS were mainly females (94.5%) and significantly older than patients with ACS (67.3 ± 13.2 years vs. 63.4 ± 12.1 years, $P < 0.001$). Physical and emotional triggers were more prevalent among the TTS population ($P < 0.001$, for both comparisons). The leading symptom on admission was chest pain, however less frequently observed in the TTS group (67.9% vs. 88.3%, $P < 0.001$), while dyspnoea was more prevalent among TTS patients (51.8% vs. 25.2%, $P < 0.001$). The upper limits of normal for troponin and brain natriuretic peptide showed higher admission values in TTS, while creatine kinase was higher in patients with ACS. Inflammatory markers were increased in both entities but not significantly different by comparison. ST-segment depression occurred less frequently in the TTS group (10.6% vs. 28.9%, $P < 0.001$) while T-wave inversion was more often noted (35.3% vs. 23.4%, $P = 0.001$). Systolic blood pressure on admission was not substantially different between groups, but higher heart rates were found in TTS (87.6 ± 23.0 b.p.m. vs. 73.3 ± 14.8 b.p.m., $P < 0.001$). Notably, the prevalence of the comorbidities cancer, COPD/asthma, and psychiatric and neurologic disorders was substantially higher in the TTS group.

Baseline characteristics of patients with TTS and ACS are shown in *Table 1*.

Takotsubo syndrome score derivation and validation

The score derivation process resulted in seven parameters ranked by relevance using their respective odds ratios (OR). Points were assigned to each criterion, depending on their diagnostic importance: female sex 25 points, emotional trigger 24 points, physical trigger 13 points, absence of ST-segment depression (except in lead aVR) 12 points, psychiatric disorders 11 points, neurologic disorders 9 points, and QTc prolongation 6 points. Points were then added in a given patient to result in a score value ranging from 0 (no criterion fulfilled) up to 100 (all criteria fulfilled; *Figure 1*).

Using a cut-off value of 40 score points, sensitivity was 89% and specificity was 91% for the presence of TTS. When patients with a score value of ≥50 were diagnosed as TTS, nearly 95% of TTS patients were diagnosed correctly (sensitivity 94.7%). When patients with a score value ≤31 were diagnosed as ACS, ~95% of ACS patients were diagnosed correctly. The logistic regression with the InterTAK Diagnostic Score as predictor yielded an intercept of −7.63 and a regression coefficient of 0.171 (SE 0.015). The corresponding OR was 1.19 (95% CI 1.15–1.22) per point. *Figure 2A* shows the predicted probabilities of TTS for the patients in the derivation cohort. The AUC of the InterTAK Diagnostic Score in

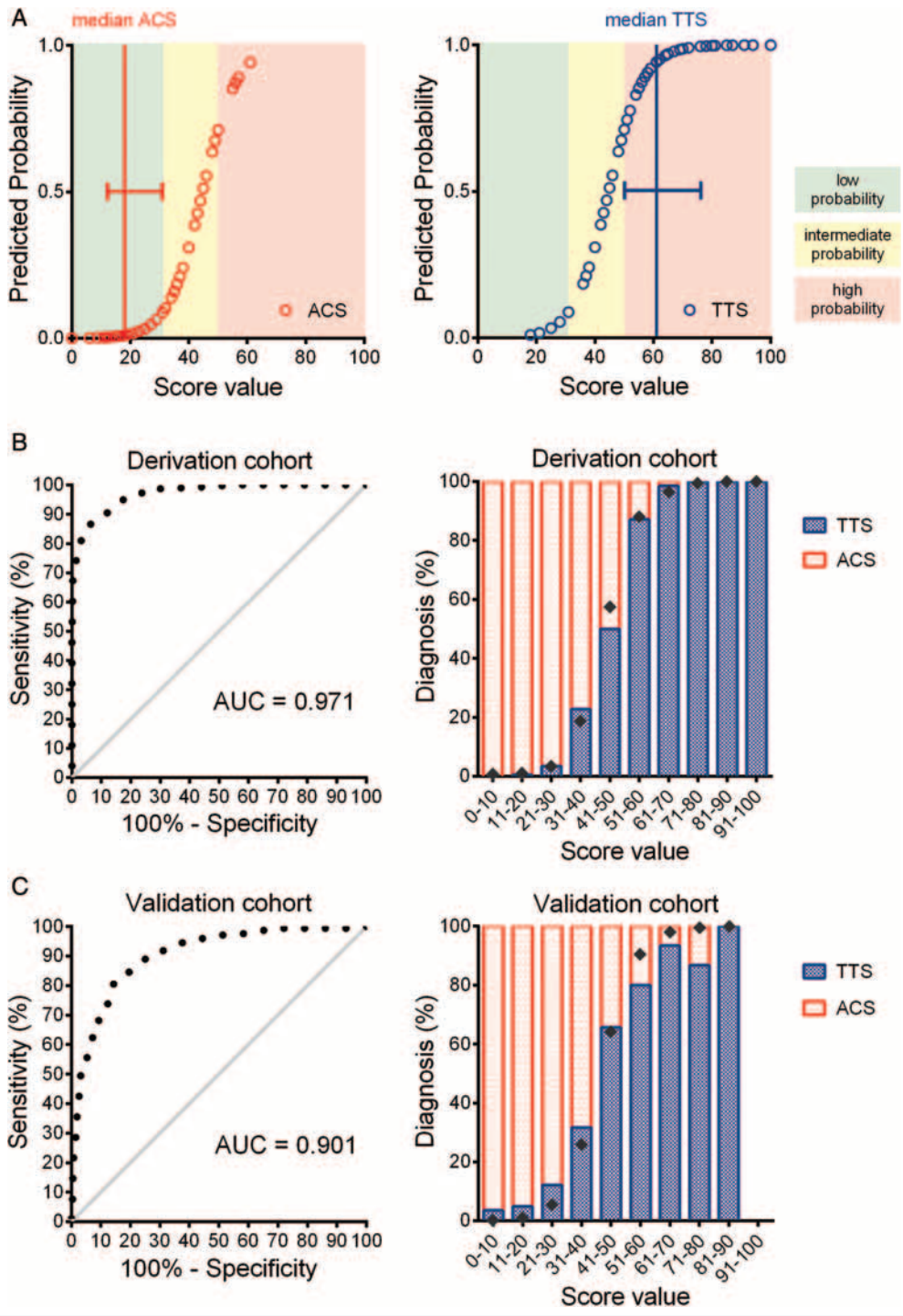

Figure 2 InterTAK Diagnostic Score for predicting the presence of takotsubo syndrome (TTS). (*A*) Relationship of risk score values (*x*-axis) and predicted probability of TTS (*y*-axis), as computed by logistic regression. Every given score value matches a predicted probability of TTS resulting in a sigmoid curve. Left: values from the acute coronary syndrome (ACS) derivation cohort (red circles). Right: values from the TTS derivation cohort (blue circles). Median and interquartile ranges in each group were drawn into the corresponding graph. When patients with a score value of ≥50 are diagnosed as TTS, nearly 95% of TTS patients are found (sensitivity 94.7%). When patients with a score value between 0 and 31 are diagnosed as ACS, almost 95% of ACS patients are diagnosed correctly (specificity 93.6%). (*B* and *C*) Receiver operating characteristic curves demonstrating an area under the curve (AUC) of 0.971 [95% confidence interval (CI) 0.96–0.98 in the derivation cohort (*B*, left)] and an AUC of 0.901 (95% CI 0.87–0.93) in the validation cohort (*C*, left)]. The graphs on the right-hand side in (*B*) and (*C*) show the percentages of TTS (blue) and ACS (red) per 10 score value points. Squares indicate the predicted probability of each corresponding bar.

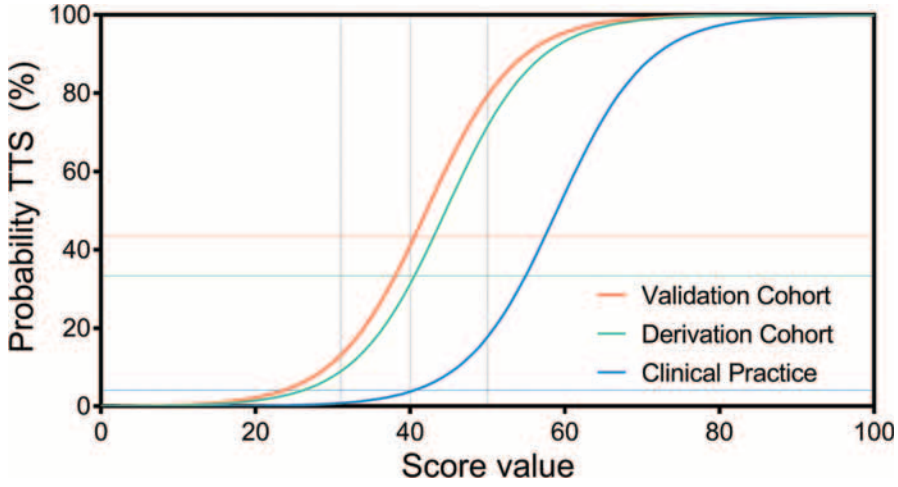

Figure 3 Predicted probability of takotsubo syndrome (TTS) corresponding to the prevalence in clinical practice. Horizontal lines indicate the prevalence of TTS in the validation cohort (orange), derivation cohort (green), and in clinical practice at the University Hospital Zurich from 2011 to 2015 (blue). Sigmoid curves show the predicted probabilities for a given score value in the derivation cohort (green), validation cohort (orange), and in clinical practice (blue).

the derivation cohort was 0.971 (95% CI 0.96–0.98) (*Figure 2B*). The right-hand panel in *Figure 2B* shows the observed and the predicted proportions of TTS patients depending on the score value. Prospective validation of the InterTAK Diagnostic Score in an independent cohort (173 TTS patients and 226 ACS patients) revealed an AUC of 0.901 (95% CI 0.87–0.93) (*Figure 2C*). The overall calibration was excellent; the mean predicted probability of TTS was 42% compared with the prevalence of 43%. The right-hand panel in *Figure 2C* shows the observed and the predicted proportions of TTS patients in the validation cohort depending on the score value.

Correction for disease prevalence

The predicted probability of TTS depends on the prevalence of the disease in clinical practice. Based on data from the leading hospital in Zurich from 2011 to 2015, we assume a prevalence of 4.1% (*Figure 3*). For each increase by 10 points, the odds increased by a factor of >5 (OR^10 = 5.5). Thus, a patient with 30 score points has a predicted probability of <1%, a patient with 50 points has a probability of 18%, and one with 60 points has a probability of >50% of suffering from TTS (*Figure 3*).

The InterTAK Diagnostic Score calculator is accessible under www.takotsubo-registry.com.

Discussion

Takotsubo syndrome is an acute heart failure syndrome and is the most important differential diagnosis of ACS due to its similar presentation in clinical symptoms, ECG, and cardiac biomarker changes. To date, no non-invasive tools are available to distinguish between both entities in the acute phase. Therefore, early cardiac catheterization is necessary to differentiate TTS from ACS.

Scoring systems are widely used in clinical medicine to help guide clinical decision-making, such as the Wells score, TIMI risk score, or the CHA_2DS_2-VASc score, among many others.[14–16] However, to date, such scoring systems are not available to distinguish TTS from ACS based on clinical parameters in the acute setting.

Therefore, in order to facilitate the initial evaluation in the emergency room prior to cardiac imaging, we developed a clinical score which estimates the probability of the presence of TTS and differentiates it from ACS. The InterTAK Diagnostic Score comprises seven clinical parameters, which can be easily obtained in the emergency department. Of note, all those parameters have previously been associated with TTS: the disease shows a strong preponderance toward female sex, with ~90% of all patients being women.[1] Emotional and physical trigger factors are a typical feature of TTS,[17] although their occurrence is not mandatory.[1,4] ST-segment depression is a common finding in ACS, but uncommon in TTS.[1,18–20] In contrast, QTc prolongation is an ECG hallmark of TTS patients.[1,18,20] The prevalence of neurologic or psychiatric disorders is twice as high in TTS compared with ACS.[1] Therefore, neurologic and psychiatric disorders may play a significant role in the development of TTS or serve as risk factors. As all these parameters can be easily obtained and were each strongly different between TTS and ACS, we reasoed that the combination of all seven parameters would result in a powerful predictive score for the diagnosis of TTS. While the InterTAK Diagnostic Score can be easily calculated on admission and would thus be helpful for initial evaluation, it provides a probability and is not diagnostic *per se*. As such, a low score does not absolutely rule out TTS, nor does a high score definitely confirm the diagnosis. Nonetheless, the InterTAK Diagnostic Score provides a probability of TTS on admission. This is of importance since TTS mimics ACS in terms of symptoms, biomarkers, and ECG findings. This score may also be valuable in clinical practice to weigh the risk and

benefit of coronary angiography, especially in old fragile patients. In addition, it may help to avoid unnecessary coronary intervention and associated platelet inhibition, for example in patients with a moderate proximal LAD stenosis and apical ballooning when risk of bleeding is present and dual antiplatlet therapy has to be avoided.

Of note, the composition of the study cohorts used for score derivation does not reflect the true prevalence of TTS. In our study, the ratio of TTS vs. ACS was 1:2 for derivation (218 patients vs. 436 patients) and 1:1.3 for validation (173 patients vs. 226 patients). However, the real life ratio for TTS vs. ACS is between 1:50 and 1:25, which means that 2–4% of patients with ACS symptoms in fact suffer from TTS and not 30% or 50% such as in our cohorts. Mathematically, correction for this bias revealed that a given score value relates to a somewhat lower probability of TTS under real-life conditions, but with a still very strong association of high values with the diagnosis of TTS.

Conclusion

The InterTAK Diagnostic Score estimates the presence of TTS with high sensitivity and distinguishes TTS from ACS with high specificity. The score can be quickly calculated in the emergency room just with clinical parameters. Prospective studies under clinical routine conditions are now needed to assess the diagnostic validity of this novel non-invasive test.

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